DRUG NAME: Enzalutamide

SYNONYM(S): MDV3100[1]

COMMON TRADE NAME(S): XTANDI®

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Enzalutamide is an androgen receptor inhibitor which acts at several steps in the androgen receptor signaling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors with more affinity than other antiandrogen agents. It also inhibits nuclear translocation of the androgen receptors, DNA binding, and coactivator recruitment. It decreases cell proliferation and induces cell death in prostate cells *in vitro* and decreases tumour volume in xenograft models. Enzalutamide lacks androgen receptor agonist activity in cell growth assays.[2]

PHARMACOKINETICS:

Oral Absorption	rapid[3]; absorption estimated at 84%; food has no clinically significant effect on extent of absorption, however peak plasma concentration may be 30% higher when fasting	
Distribution	extensive extravascular distribution	
	cross blood brain barrier?	yes, including active metabolite
	volume of distribution	110 L
	plasma protein binding	parent (97-98%), primarily to albumin ; metabolites (95-98%)
Metabolism	extensively metabolized; substrate of CYP 2C8 and to a lesser extent CYP 3A4/5	
	active metabolite(s)	N-desmethyl enzalutamide (M2); primarily via CYP 2C8
	inactive metabolite(s)	carboxylic acid derivative (M1) primarily; up to 7 other unnamed phase I metabolites
Excretion	primarily via renal excretion of hepatic metabolites	
	urine	71% (primarily as M1; trace amounts of enzalutamide and M2)
	feces	14% (<1% as unchanged enzalutamide)
	terminal half life	5.8 days
	clearance	0.56 L/h (range 0.33 to 1.02 L/h)[4]
Elderly	no meaningful differences[4]	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to enzalutamide, sorbitol, or fructose.[2]
- women who are pregnant, may become pregnant, or are lactating.[2]

Caution:
- not intended for use in women.[2]
- associated with ***neuropsychiatric events*** (i.e., seizure, memory impairment, and hallucination); caution is required for activities where mental impairment or sudden loss of consciousness may cause serious harm[2]
- concurrent medication should be carefully reviewed for ***potential drug interactions***, particularly in regard to CYP 3A4, CYP 2C8, CYP 2C9, and CYP 2C19; dose adjustment may be required.[2] See paragraphs in **Interactions** section.
- associated with ***QT prolongation***[2]; monitor ECG and electrolytes and use cautiously in patients with known history of QT prolongation, risk factors for torsades de pointes, or taking medications known to prolong the QT interval. See paragraph in **Interactions** section.
- associated with increases in systolic and diastolic ***blood pressure***, increased risk of hypertension, and worsening of pre-existing hypertension[2]

Carcinogenicity: Long-term animal studies have not been conducted.[2]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Enzalutamide is not clastogenic in mammalian *in vivo* chromosome tests.[2]

Fertility: Reproductive organ changes were seen in studies in mice, rats, and dogs. In rats, observed changes included atrophy of the prostate, seminal vesicles, and mammary glands in males, and pituitary and mammary gland hyperplasia in females. In dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed.[2]

Pregnancy: FDA Pregnancy Category X.[4] Studies in animals or humans have shown fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. Contraindicated in women who are or may become pregnant.
There is no human data in pregnancy, however maternal use is expected to produce changes in hormone levels which could affect the development of the fetus. In mice, enzalutamide induced premature deliveries, embryo-fetal deaths, and external and skeletal abnormalities (including cleft palate). It is not known if enzalutamide or its metabolites are present in semen. Appropriate contraception is recommended during treatment and for three months after treatment with enzalutamide. Condoms are recommended during sexual activity with pregnant women; condoms plus a second effective contraceptive method are recommended during sexual activity with women of child-bearing potential.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[5] When placebo-controlled trials are available, adverse events will generally be included if the incidence is $\geq$5% higher in the treatment group.[1,2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	neutropenia (15%, severe 1%)
gastrointestinal	*emetogenic potential: rare*[6]
	diarrhea[1] (21%, severe 1%)
general disorders and administration site conditions	***fatigue*** (34-51%, severe 6%)[2,3]
	peripheral edema[4] (15%, severe 1%)
infections and infestations	infection, miscellaneous[3] (≤6%)
	lower respiratory infection[3,4] (9%, severe 2%)
	upper respiratory infection[3] (11%)
injury, poisoning, and procedural complications	bone fractures, non-pathological (4%)
	falls (4-5%, severe <1%)[2,3]; not associated with loss of consciousness or seizure
investigations	ALT abnormalities (10%, severe <1%)
	AST abnormalities (23%, severe <1%)
	hyperbilirubinemia[3] (3%)
	QT prolongation[1,2]
musculoskeletal and connective tissue	arthralgia[3] (21%)
	back pain[3] (26%)
	muscle weakness[3] (10%)
	musculoskeletal pain[1] (14%, severe 1%)
nervous system	dizziness[3] (10%)
	headache (12%, severe 1%)
	hypoesthesia[3] (4%)
	mental impairment, including amnesia, cognitive disorder, memory impairment (4%)
	paresthesia[3] (7%)
	seizures (1%); see paragraph following **Side Effects** table
psychiatric	anxiety (6-7%, severe <1%)
	hallucinations[3] (2%)
	insomnia[3] (9%)
renal and urinary	hematuria[3] (7%)
respiratory, thoracic and mediastinal	epistaxis[3] (3%)
skin and subcutaneous tissue	dry skin (4%)
	pruritus (4%)
vascular	hot flush (20%)
	hypertension (6%, severe 2%); see paragraph following **Side Effects** table

Adapted from standard reference[2] unless specified otherwise.

Hypertension, increased systolic and diastolic blood pressure, or hypertensive crisis occurs in approximately 7% of patients. Hypertension rarely leads to discontinuation or dose modification of enzalutamide, however approximately 75% of patients reporting hypertension will require either initiation of antihypertensive treatment or an increase in the dose of their current therapy.[2]

An increased risk of ***seizure*** has been associated with enzalutamide; reported onset is1-20 months after treatment initiation. Doses higher than 160 mg may be associated with a greater risk of seizure. Seizures resolved after treatment cessation. Both enzalutamide and its active metabolite cross the blood brain barrier, where they bind to and inhibit the activity of the GABA-gated chloride channel, an off-target mechanism associated with the onset of seizure in animals. It is not clear if history of seizure or other predisposing factors increases the risk of seizure with enzalutamide, therefore, caution is advised when using enzalutamide in this group.[2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
gemfibrozil[2]	2 fold increase in AUC of enzalutamide	inhibition of CYP 2C8 by gemfibrozil	avoid concurrent use if possible; otherwise, a 50% dose reduction for enzalutamide is recommended
itraconazole[2]	1 fold increase in AUC of enzalutamide	inhibition of CYP 3A4 by itraconazole	monitor for side effects of enzalutamide; dose adjustment is not required
midazolam[2]	86% decrease in AUC of midazolam	induction of CYP 3A4 by enzalutamide	avoid concurrent use
omeprazole[2]	70% decrease in AUC of omeprazole	induction of CYP 2C19 by enzalutamide	avoid concurrent use
warfarin[2]	56% decrease in AUC of S-warfarin	induction of CYP 2C9 by enzalutamide	monitor INR; adjust dose of warfarin as needed

NOTE: effects on enzymes ***may persist for one month*** or longer after discontinuation of enzalutamide due to the long half-life of enzalutamide.[2]

Enzalutamide has been associated with statistically significant **QTc prolongation** (mean increase of 3-5.6 msec from baseline during weeks 5-25). Use caution during concurrent therapy with drugs that prolong QT/QT_c interval. Consider monitoring ECG and serum electrolytes for patients at risk for QTc prolongation.[2]

Enzalutamide is a **substrate** of CYP 2C8. If co-administered with strong CYP 2C8 inhibitors, reduce enzalutamide starting dose to 80 mg once daily. Strong inducers of CYP 2C8 may reduce the effectiveness of enzalutamide and should be avoided if possible.[2]

Enzalutamide is a strong **inducer** of CYP 3A4 and a moderate inducer of CYP 2C9 and CYP 2C19. Co-administration may result in decreased exposure to substrates of these enzymes. Avoid co-administration with substrates with a narrow therapeutic index if possible. Dose adjustment of the substrate may be required to maintain therapeutic concentrations and additional monitoring may be required.[2]

Enzalutamide is a **substrate** of CYP 3A4. Dose adjustment of enzalutamide is not necessary when co-administered with CYP 3A4 inhibitors. Grapefruit or grapefruit juice may inhibit CYP 3A4 metabolism in the intestinal wall, and theoretically may increase the plasma level of enzalutamide, however, avoiding grapefruit or grapefruit juice does not appear to be necessary during treatment. The effect of CYP 3A4 inducers has not been studied *in vivo*.[2]

In vitro studies suggest that enzalutamide may **induce** uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) and decrease exposure to substrates of this enzyme. Avoid co-administration with UGT1A1 substrates with a narrow therapeutic index.[2]

Enzalutamide has been reported to have both an inhibiting and an inducing effect on P-glycoprotein *in vitro* and has been reported to inhibit breast cancer resistant protein (BRCP) and multidrug resistance-associated protein 2 (MRCP2) *in vitro.* These effects have not been evaluated *in vivo*; clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Astellas Pharma Canada, Inc. supplies enzalutamide as 40 mg liquid filled capsules. Capsules contain sorbitol. Store at room temperature.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral[2]:	Cycle Length: ***160 mg*** (range 80-160 mg) ***PO once daily***. Administer with food or on an empty stomach. Do not crush or chew capsules.
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure:	no adjustment required in mild to moderate renal impairment (calculated creatinine clearance ≥ 30 mL/min)[2]; no information found in severe impairment Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	no adjustment required in mild to moderate impairment[2]; no information found in severe impairment
Dosage in dialysis:	unlikely to be significantly removed by intermittent hemodialysis or continuous ambulatory peritoneal dialysis due to its large volume of distribution and low unbound free fraction[2]

Children: no information found

REFERENCES:

1. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187-1197.
2. Astellas Pharma Canada Inc. XTANDI® product monograph. Markham, Ontario; 28 May 2013.
3. Lexi-Drugs. Lexi-Comp Online® (database on the Internet). Enzalutamide. Lexi-Comp Inc., 25 June 2013. Available at: http://online.lexi.com. Accessed 26 June 2013.
4. Astellas Pharma US Inc. XTANDI® product monograph. Northbrook, Illinois; August 2012.
5. Kim Chi MD. Personal communication. BC Cancer Agency Genitourinary Tumour Group; 7 August 2013.
6. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.